Please add the following new claims:

--21. An aqueous RNA ~~isolation~~ extraction reagent, comprising at least one nonionic detergent at a concentration of 0.1-1.0% (vol/vol), at least one phenol at a concentration of 10-60% (wgt/vol) and at least one phenol solubilizer at a concentration of 15-55% (vol/vol).

--22. An aqueous RNA ~~isolation~~ extraction reagent, comprising at least one nonionic detergent at a concentration of 0.1-1.0% (vol/vol), at least one phenol at a concentration of 10-60% (wgt/vol) and at least one chelator at a concentration of 0.02-0.25 M.--.

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 2-22 are pending in the application, with claims 21 and 22 being the independent claims. Claim 1 is sought to be canceled without prejudice to or disclaimer of the subject matter therein. New claims 21 and 22 are sought to be added. New claims 21 and 22 are supported by as-filed claim 1 and by page 4 of the specification, lines 15-19. The amendments to the specification correct typographical errors and designate trademarks. The amendments to the claims more clearly define the claimed invention, correct typographical errors, correct Markush groups, designate trademarks and correct claim dependency. The amendments are believed to introduce no new matter and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-20 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner stated that the claimed RNA isolation reagent appears to require at least a phenol, non-ionic detergent and chelating agent. Applicant respectfully traverses the rejection.

The claimed RNA isolation reagents contain either a non-ionic detergent, phenol and phenol solubilizer as set forth in claim 21, or a non-ionic detergent, phenol and chelator as set forth in claim 22. The chelating agent may be included in the reagent as indicated in claim 22, but contrary to the Examiner's assertion, it is not a required component.

As noted on page 4 of the specification, the chelator protects the extracted RNA from degradation by magnesium ions (when present) and protects RNA from RNAses. However, the phenol also functions as an RNA protector and thus, the chelator is not a required component.

Applicant submits that the rejection has been overcome. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 1-20 under 35 U.S.C. § 103 as being unpatentable over Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1989)) in view of Chomczynski (U.S. Patent No. 5,346,994). Applicant respectfully traverses the rejection.

The Examiner asserted that Sambrook *et al.* teach a method of isolating RNA using a non-ionic detergent, phenol and RNAse inhibitor, but fail to teach the use of a phenol solubilizer or chelator to inhibit RNA degradation. The Examiner cited Chomczynski to teach that the use of a phenol, at a concentration of 30-50%, and a phenol solubilizer, at a concentration of 3-15%, is known. Finally, the Examiner cited DeBonville *et al.* (U.S. Patent No. 4,833,239) to illustrate that the use of a phenol stabilizer, such as 8-hydroxyquinoline, and a phenol solubilizer are known.

The Examiner acknowledged that the references cited do not teach the use of a chelator. However, the Examiner stated that the inclusion of a chelating agent would have been obvious since ribonuclease has a zinc ion at the catalytic site, and that a strong chelating agent at a high concentration would "starve the enzyme" of the zinc ion. Office Action, page 3, line 2. The Examiner concluded that the claimed reagent would have been obvious to one of ordinary skill in the art needing to rapidly purify RNA in the absence of an expensive RNAse inhibitor.

The claimed RNA isolation reagent of independent claim 21 contains at least one non-ionic detergent, at least one phenol and at least one phenol solubilizer, and the claimed RNA isolation reagent of independent claim 22 contains at least one non-ionic detergent, at least one phenol and at least one chelator. The references cited by the Examiner, either alone or in combination, fail to teach or suggest an RNA isolation reagent containing the claimed combination of ingredients. The references do not contain the requisite motivation to combine and do not provide a reasonable expectation of success of obtaining the claimed invention. Both motivation and expectation of success are necessary to establish a *prima facie* case of obviousness. *In re Vaeck*, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991).

The Examiner's primary reference, Sambrook *et al.*, teaches a method of isolating RNA using an extraction buffer containing, *inter alia*, a detergent and RNAse inhibitor or vanadyl-

ribonucleoside complex. The extraction buffer does not contain a phenol, phenol solubilizer, chelator or non-ionic detergent. It is noted that Sambrook *et al.* extract proteins with a phenol:chloroform reagent, however, that reagent is not used to extract RNA and is not a component of the RNA extraction buffer. *See* pages 7.6-7.7.

Chomczynski, the secondary reference, teaches an RNA, DNA and protein solvent solution containing chaotropic agents, a phenol, a phenol solubilizer and a buffer. The solution does not contain a non-ionic detergent or chelator.

Apparently, since Sambrook *et al.* and Chomczynski both disclose solutions employed in RNA isolation methods, the Examiner combined the two references in an attempt to recreate the claimed RNA isolation reagents. However, the Examiner failed to provide the motivation required to combine Sambrook *et al.* and Chomczynski and instead, reconstructed the invention by picking and choosing isolated teachings from the references. In doing so, the Examiner disregarded the fact that the references must be considered as a whole. One skilled in the art would not combine the Chomczynski solution for extracting RNA, DNA and proteins with the Sambrook *et al.* buffer for extracting RNA because, *inter alia*, the inclusion of a chaotropic agent, as taught by Chomczynski, in the Sambrook *et al.* buffer would cause co-isolation of polysaccharides so that the resulting RNA would not be in a purified form.

The third reference cited by the Examiner, DeBonville *et al.*, does not cure the deficiencies of Sambrook *et al.* or Chomczynski. The DeBonville *et al.* patent is directed to methods of isolating DNA, *not* RNA. The DNA reagent composition contains, *inter alia*, phenol, isoamyl alcohol and 8-hydroxyquinoline. This composition does not contain the ingredients required to isolate RNA as set forth in the claimed reagents. Moreover, the reference is not analogous to the claimed invention or to the Sambrook *et al.* and Chomczynski references. One skilled in the art

would not use a DNA isolation reagent to isolate RNA. As noted by DeBonville *et al.*, the DNA isolation method requires the addition of Rnase A which degrades RNA. Clearly, one isolating RNA would not follow the DNA isolation methods outlined in the DeBonville *et al.* patent and would not combine such methods with any RNA isolation method.

The Examiner's statement regarding the alleged obvious inclusion of a chelator has been noted. The Examiner failed to provide a reference asserting that the inclusion of a chelator in an RNA isolation reagent is known. Moreover, the fact that ribonuclease has a zinc ion at the catalytic site is insufficient motivation to add a chelator to an RNA isolation reagent, especially in view of the art cited wherein RNA isolation methods *require* an RNAse inhibitor, vanadyl-ribonucleoside complex or chaotropic agent and do not rely on the deprivation of ribonuclease of a zinc ion.

The Examiner failed to point out any teaching in the art which would suggest which isolation reagent components are critical, or which would provide guidance leading to appropriate changes necessary to obtain the claimed invention. As a result, one skilled in the art would have *no* direction concerning how to successfully obtain the claimed invention. Contrary to the Examiner's viewpoint, simply because a piece of art, by itself, may allegedly teach *any* nucleic acid or protein isolation, this fails to render the claimed invention obvious. Further, the motivation to combine references must be present before combining the art, not after one has already decided what they wish the combination to show.

The references cited do not teach or suggest the claimed RNA isolation reagents. The primary reference, Sambrook *et al.*, fails to teach or suggest the claimed invention for the reasons indicated above. This failure is not remedied by the secondary references, Chomczynski and

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DeBonville *et al.* Thus, the combination of Sambrook *et al.* in view of Chomczynski and DeBonville *et al.* does not render the claimed invention obvious.

Applicant submits that the rejection has been overcome. Withdrawal of the rejection is respectfully requested.

Conclusion

All of the stated grounds rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

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Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert W. Esmond

Robert W. Esmond
Attorney for Applicant
Registration No. 32,893

Date: June 3, 1999

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600
P:\USERS\kvidovic\0942\3840001\p91-15.wpd

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